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(54) Title: **AZETIDINE, PYRROLIDINE AND PIPERIDINE DERIVATIVES**

(57) Abstract

A class of substituted azetidine, pyrrolidine and piperidine derivatives, linked by a fluoro-substituted alkylene chain to a fused bicyclic heteroaromatic moiety such as indolyl, are selective agonists of 5-HT₁-like receptors, being potent agonists of the human 5-HT_{1D} receptor subtype whilst possessing at least a 10-fold selective affinity for the 5-HT_{1D} receptor subtype relative to the 5-HT_{1D} subtype; they are therefore useful in the treatment and/or prevention of clinical conditions, in particular migraine and associated disorders, for which a subtype-selective agonist of 5-HT_{1D} receptors is indicated, whilst eliciting fewer side-effects, notably adverse cardiovascular events, than those associated with non-subtype-selective 5-HT_{1D} receptor agonists.

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AZETIDINE, PYRROLIDINE AND PIPERIDINE DERIVATIVES

The present invention relates to a class of substituted azetidine, pyrrolidine and piperidine derivatives which act on 5-hydroxytryptamine 5 (5-HT) receptors, being selective agonists of so-called "5-HT₁-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

It has been known for some time that 5-HT₁-like receptor agonists which exhibit selective vasoconstrictor activity are of use in the treatment 10 of migraine (see, for example, A. Doenicke *et al.*, *The Lancet*, 1988, Vol. 1, 1309-11; and W. Feniuk and P.P.A. Humphrey, *Drug Development Research*, 1992, 26, 235-240).

The human 5-HT₁-like or 5-HT_{1D} receptor has recently been shown by molecular cloning techniques to exist in two distinct subtypes. These 15 subtypes have been termed 5-HT_{1Dα} (or 5-HT_{1D-1}) and 5-HT_{1Dβ} (or 5-HT_{1D-2}), and their amino acid sequences are disclosed and claimed in WO-A-91/17174.

The 5-HT_{1Dα} receptor subtype in humans is believed to reside on sensory terminals in the dura mater. Stimulation of the 5-HT_{1Dα} subtype 20 inhibits the release of inflammatory neuropeptides which are thought to contribute to the headache pain of migraine. The human 5-HT_{1Dβ} receptor subtype, meanwhile, is located predominantly on the blood vessels and in the brain, and hence may play a part in mediating constriction of cerebral and coronary arteries, as well as CNS effects.

25 Administration of the prototypical 5-HT_{1D} agonist sumatriptan (GR43175) to humans is known to give rise at therapeutic doses to certain adverse cardiovascular events (see, for example, F. Willett *et al.*, *Br. Med. J.*, 1992, 304, 1415; J.P. Ottenvanger *et al.*, *The Lancet*, 1993, 341, 861-2; and D.N. Bateman, *The Lancet*, 1993, 341, 221-4). Since sumatriptan 30 barely discriminates between the human 5-HT_{1Dα} and 5-HT_{1Dβ} receptor subtypes (cf. WO-A-91/17174, Table 1), and since it is the blood vessels

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with which the 5-HT_{1D_B} subtype is most closely associated, it is believed that the cardiovascular side-effects observed with sumatriptan can be attributed to stimulation of the 5-HT_{1D_B} receptor subtype. It is accordingly considered (cf. G.W. Rebeck *et al.*, *Proc. Natl. Acad. Sci. USA*, 1994, **91**, 5 3666-9) that compounds which can interact selectively with the 5-HT_{1D_A} receptor subtype, whilst having a less pronounced action at the 5-HT_{1D_B} subtype, might be free from, or at any rate less prone to, the undesirable cardiovascular and other side-effects associated with non-subtype-selective 5-HT_{1D} receptor agonists, whilst at the same time maintaining a beneficial 10 level of anti-migraine activity.

The compounds of the present invention, being selective 5-HT₁-like receptor agonists, are accordingly of benefit in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension 15 headache and paediatric migraine. In particular, the compounds according to this invention are potent agonists of the human 5-HT_{1D_A} receptor subtype. Moreover, the compounds in accordance with this invention have been found to possess at least a 10-fold selective affinity for the 5-HT_{1D_A} receptor subtype relative to the 5-HT_{1D_B} subtype, and they 20 can therefore be expected to manifest fewer side-effects than those associated with non-subtype-selective 5-HT_{1D} receptor agonists.

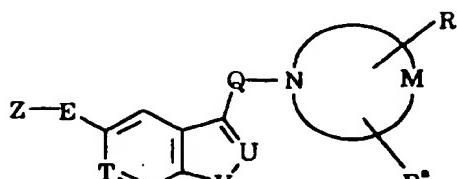
Several distinct classes of substituted five-membered heteroaromatic compounds are described in published European patent applications 0438230, 0494774 and 0497512, and published International 25 patent applications 93/18029, 94/02477 and 94/03446. The compounds described therein are stated to be agonists of 5-HT₁-like receptors, and accordingly to be of particular use in the treatment of migraine and associated conditions. None of these publications, however, discloses nor even suggests the azetidine, pyrrolidine and piperidine derivatives 30 provided by the present invention.

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- In EP-A-0548813 is described a series of alkoxy pyridin-4-yl and alkoxy pyrimidin-4-yl derivatives of indol-3-ylalkylpiperazines which are alleged to provide treatment of vascular or vascular-related headaches, including migraine. There is, however, no disclosure nor any suggestion
- 5 in EP-A-0548813 of replacing the precisely substituted piperazine moiety described therein with a differently substituted azetidine, pyrrolidine or piperidine moiety; nor is there any suggestion therein that the alkylene chain present in the indol-3-ylalkylpiperazine portion of the molecule might be substituted with one or more fluorine atoms.
- 10 WO-A-91/18897 describes a class of tryptamine derivatives substituted by various five-membered rings, which are stated to be specific to a particular type of "5-HT₁-like" receptor and thus to be effective agents for the treatment of clinical conditions, particularly migraine, requiring this activity. A further class of tryptamine derivatives with alleged anti-
- 15 migraine activity is disclosed in WO-A-94/02460. However, neither WO-A-91/18897 nor WO-A-94/02460 discloses or suggests the azetidine, pyrrolidine and piperidine derivatives provided by the present invention.
- Moreover, nowhere in the prior art mentioned above is there any disclosure of a subtype-selective 5-HT_{1D} receptor agonist having a 5-HT_{1D_a} receptor binding affinity (IC₅₀) below 50 nM and at least a 10-fold selective affinity for the 5-HT_{1D_a} receptor subtype relative to the 5-HT_{1D_b} subtype.
- The compounds according to the present invention are subtype-selective 5-HT_{1D} receptor agonists having a human 5-HT_{1D_a} receptor binding affinity (IC₅₀) below 50 nM, typically below 10 nM and preferably
- 20 below 1 nM; and at least a 10-fold selective affinity, typically at least a 50-fold selective affinity and preferably at least a 100-fold selective affinity, for the human 5-HT_{1D_a} receptor subtype relative to the 5-HT_{1D_b} subtype. Moreover, the compounds in accordance with this invention possess interesting properties in terms of their efficacy and/or
- 25 bioavailability.

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The present invention provides a compound of formula I, or a salt or prodrug thereof:

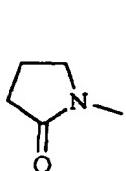


(I)

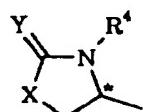
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wherein

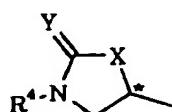
- Z represents hydrogen, halogen, cyano, nitro, trifluoromethyl, -OR⁵, -OCOR⁵, -OCONR⁵R⁶, -OCH₂CN, -OCH₂CONR⁵R⁶, -SR⁵, -SOR⁵, -SO₂R⁵, -SO₂NR⁵R⁶, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁶, -COR⁵, -CO₂R⁵, 10 -CONR⁵R⁶, or a group of formula (Za), (Zb), (Zc) or (Zd):



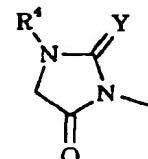
(Za)



(Zb)



(Zc)



(Zd)

in which the asterisk * denotes a chiral centre; or

- 15 Z represents an optionally substituted five-membered heteroaromatic ring selected from furan, thiophene, pyrrole, oxazole, thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole and tetrazole;

X represents oxygen, sulphur, -NH- or methylene;

- 20 Y represents oxygen or sulphur;

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

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Q represents a straight or branched alkylene chain containing from 1 to 6 carbon atoms, substituted in any position by one or more fluorine atoms;

- T represents nitrogen or CH;
- 5 U represents nitrogen or C-R²;
- V represents oxygen, sulphur or N-R³;
- R², R³ and R⁴ independently represent hydrogen or C₁₋₆ alkyl;
- R⁵ and R⁶ independently represent hydrogen, C₁₋₆ alkyl, trifluoromethyl, phenyl, methylphenyl, or an optionally substituted 10 aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl group; or R⁵ and R⁶, when linked through a nitrogen atom, together represent the residue of an optionally substituted azetidine, pyrrolidine, piperidine, morpholine or piperazine ring;
- M represents the residue of an azetidine, pyrrolidine or piperidine 15 ring;
- R represents a group of formula -W-R¹;
- W represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally substituted in any position by a hydroxy group;
- 20 R¹ represents -OR^x, -SR^x, -SOR^x, -SO₂R^x or -NR^xR^y;
- R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group; or R^x and R^y together represent a C₂₋₆ alkylene group, which alkylene group may be optionally substituted by one or more substituents selected from C₁₋₆ alkyl, aryl and hydroxy, or fused with a 25 phenyl ring; and
- R^x represents hydrogen, hydroxy, hydrocarbon or a heterocyclic group.
- Where Z in the compounds of formula I above represents a five-membered heteroaromatic ring, this ring may be optionally substituted by 30 one or, where possible, two substituents. As will be appreciated, where Z represents an oxadiazole, thiadiazole or tetrazole ring, only one

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substituent will be possible; otherwise, one or two optional substituents may be accommodated around the five-membered heteroaromatic ring Z. Examples of suitable substituents on the five-membered heteroaromatic ring Z include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl, 5 aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, halogen, cyano or trifluoromethyl.

When R⁵ and R⁶, when linked through a nitrogen atom, together represent the residue of an azetidine, pyrrolidine, piperidine, morpholine 10 or piperazine ring, this ring may be unsubstituted or substituted by one or more substituents. Examples of suitable substituents include C₁₋₆ alkyl, aryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxycarbonyl and C₁₋₆ alkylaminocarbonyl. Typical substituents include methyl, benzyl, methoxy, methoxycarbonyl, ethoxycarbonyl and methylaminocarbonyl. In 15 particular, where R⁵ and R⁶ together represent the residue of a piperazine ring, this ring is preferably substituted on the distal nitrogen atom by a C₂₋₆ alkoxycarbonyl moiety such as methoxycarbonyl or ethoxycarbonyl.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in 20 the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable 25 acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof 30 may include alkali metal salts, e.g. sodium or potassium salts; alkaline

earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up 5 to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, indanyl, aryl and aryl(C₁₋₆)alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom 10 preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl and heteroaryl(C₁₋₆)alkyl groups.

15 Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl, isobutyl, tert-butyl and 2,2-dimethylpropyl.

20 Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl and dimethylallyl groups.

25 Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Typical examples of C₃₋₇ cycloalkyl(C₁₋₆)alkyl groups include cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl.

30 Particular indanyl groups include indan-1-yl and indan-2-yl. Particular aryl groups include phenyl and naphthyl.

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Particular aryl(C₁₋₆)alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl groups.

5 Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

10 The expression "heteroaryl(C₁₋₆)alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl and isoquinolinylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C₁₋₆ alkyl, adamantly, phenyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ aminoalkyl, trifluoromethyl, hydroxy, 20 C₁₋₆ alkoxy, aryloxy, keto, C₁₋₃ alkylenedioxy, nitro, cyano, carboxy, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, C₂₋₆ alkylcarbonyloxy, arylcarbonyloxy, aminocarbonyloxy, C₂₋₆ alkylcarbonyl, arylcarbonyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphanyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, -NR^vR^w, -NR^vCOR^w, -NR^vCO₂R^w, -NR^vSO₂R^w, -CH₂NR^vSO₂R^w, -NHCONR^vR^w, 25 -CONR^vR^w, -SO₂NR^vR^w and -CH₂SO₂NR^vR^w, in which R^v and R^w independently represent hydrogen, C₁₋₆ alkyl, aryl or aryl(C₁₋₆)alkyl, or R^v and R^w together represent a C₂₋₆ alkylene group.

When R^x and R^y, or R^v and R^w, together represent a C₂₋₆ alkylene group, this group may be an ethylene, propylene, butylene.

30 pentamethylene or hexamethylene group, preferably butylene or pentamethylene.

When R^x and R^y together represent a C₂₋₆ alkylene group, this group may be unsubstituted or substituted by one or more substituents selected from C₁₋₆ alkyl, aryl and hydroxy. Typical substituents include methyl, phenyl and hydroxy.

5 Furthermore, when R^x and R^y together represent a C₂₋₆ alkylene group, this group may optionally be fused with a phenyl ring. In this context, a typical group of formula -NR^xR^y as defined for the substituent R¹ is 1,2,3,4-tetrahydroisoquinolinyl.

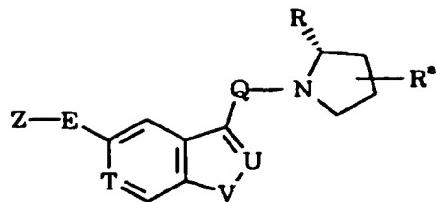
The term "halogen" as used herein includes fluorine, chlorine, 10 bromine and iodine, especially fluorine.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional 15 procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the 20 compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. For example, the compounds of formula I above wherein Z represents a group of formula (Zb) or (Zc) have a chiral centre denoted by the asterisk *, which may accordingly be in the (R) or (S) configuration. It is to be understood that 25 all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In particular, where M represents the residue of a pyrrolidine ring, and the substituent R is attached to the 2-position thereof, then the absolute stereochemical configuration of the carbon atom at the point of 30 attachment of the moiety R is preferably as depicted in structure IA as follows:

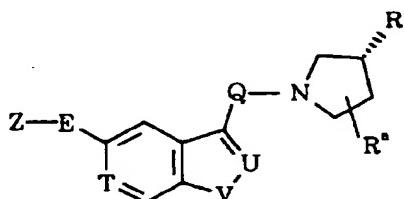
- 10 -



(IA)

wherein Z, E, Q, T, U, V, R and R* are as defined above.

- Moreover, where M represents the residue of a pyrrolidine ring, and the substituent R is attached to the 3-position thereof, then the absolute 5 stereochemical configuration of the carbon atom at the point of attachment of the moiety R is preferably as depicted in structure IB as follows:



(IB)

wherein Z, E, Q, T, U, V, R and R* are as defined above.

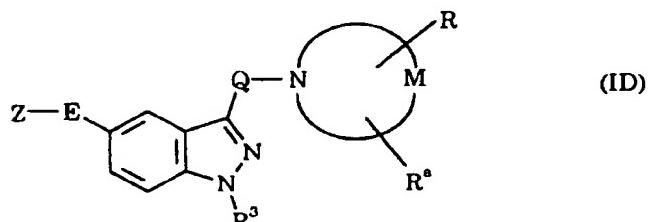
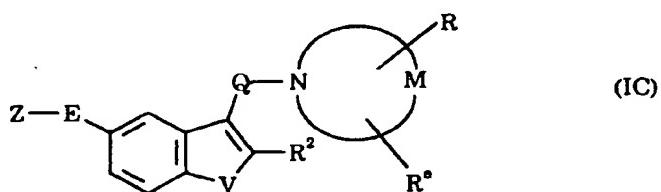
- Where E and W, which may be the same or different, represent 10 straight or branched alkylene chains, these may be, for example, methylene, ethylene, 1-methylethylene, propylene, 2-methylpropylene or butylene. In addition, W may be substituted in any position by a hydroxy group giving rise, for example, to a hydroxymethyl-methylene, 2-hydroxypropylene or 2-hydroxymethyl-propylene linkage. Moreover, E 15 and W may each independently represent a chemical bond. Where E represents a chemical bond, the moiety Z is attached directly to the central fused bicyclic heteroaromatic ring system containing the variables T, U and V. Similarly, where W represents a chemical bond, the substituent R* is attached directly to the azetidine, pyrrolidine or piperidine ring of 20 which M is the residue.

Suitably, E represents a chemical bond or a methylene linkage.

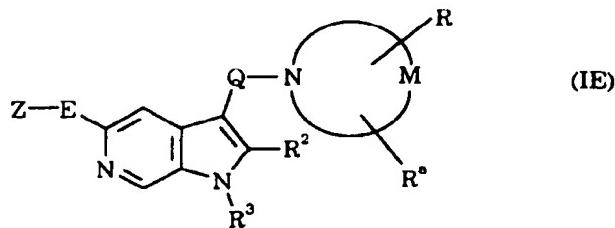
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The alkylene chain Q is substituted in any position by one or more fluorine atoms, preferably by one or two fluorine atoms and more preferably by one fluorine atom. Representative alkylene chains for Q include 2-fluoropropylene, 2,2-difluoropropylene and 2-fluoromethyl-propylene, especially 2-fluoropropylene or 2-fluoromethyl-propylene.

5 The compound of formula I in accordance with the present invention is suitably an indole, benzofuran or benzothiophene derivative of formula IC, an indazole derivative of formula ID, or a pyrrolo[2,3-c]-pyridine derivative of formula IE:

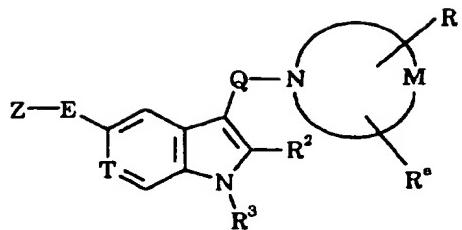


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wherein Z, E, Q, V, M, R, R^a, R² and R³ are as defined above. Preferably, the compounds according to the invention are indole or pyrrolo[2,3-c]-pyridine derivatives of formula IF:

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wherein Z, E, Q, T, M, R, R^x, R² and R³ are as defined above, in particular wherein R² and R³ are both hydrogen.

Suitably, W represents a chemical bond or a methylene or

- 5 hydroxymethyl-methylene linkage, in particular a chemical bond or a methylene linkage.

Suitably, R^x and R^y independently represent hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, indanyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents selected typically from C₁₋₆ alkyl, halogen, hydroxy, C₁₋₆ alkoxy, aminocarbonyloxy, amino, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulphonylamino and C₁₋₆ alkylaminosulphonylmethyl. Particular values of R^x and R^y include hydrogen, methyl, hydroxyethyl, isobutyl, 2,2-dimethylpropyl, allyl, dimethylallyl, 1-cyclohexylethyl, 2-cyclohexylethyl, indanyl, hydroxy-indanyl, phenyl, benzyl, methyl-benzyl, fluorobenzyl, methoxy-benzyl, acetylamino-benzyl, 1-phenylethyl, 2-phenylethyl, 2-hydroxy-1-phenylethyl, 2-methoxy-1-phenylethyl, 2-aminocarbonyloxy-1-phenylethyl, 1-(fluorophenyl)ethyl, 1-(fluorophenyl)-2-hydroxyethyl, 1-(fluorophenyl)-2-methoxyethyl, 1-(acetylamino-phenyl)ethyl, 2-(acetylamino-phenyl)ethyl, 2-hydroxy-1-phenylprop-1-yl, 1-phenylprop-2-yl, 2-phenylprop-2-yl, 1-hydroxy-1-phenylprop-2-yl, 1-hydroxy-2-phenylprop-2-yl, 1-hydroxy-3-phenylprop-2-yl, furylmethyl, thienylmethyl and pyridylmethyl, especially hydrogen, methyl, benzyl or 1-(fluorophenyl)-2-hydroxyethyl.

- 25 In addition, where R^x and R^y together represent an optionally substituted or phenyl ring-fused C₂₋₆ alkylene group, the substituent

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$\text{-NR}^x\text{R}^y$ as defined for R^1 may suitably represent 3,3-dimethylpiperidinyl, 2-phenylpiperidinyl, 3-hydroxy-2-phenylpiperidinyl or 1,2,3,4-tetrahydroisoquinolin-2-yl.

- Suitable values for the substituent R^1 include hydroxy, benzyloxy,
- 5 methoxy-benzyloxy, pyridylmethoxy, benzylthio, fluorobenzyl-thio, phenylsulphanyl, benzylsulphanyl, fluorobenzyl-sulphanyl, fluorobenzyl-sulphonyl, amino, methylamino, indanylamino, hydroxyindanyl-amino, benzylamino, N -(methylbenzyl)-amino, N -(acetylamino-benzyl)-amino, N -(1-phenylethyl)-amino, N -(2-phenylethyl)-amino, N -(2-hydroxy-1-phenylethyl)-amino, N -(2-methoxy-1-phenylethyl)-amino, N -(2-aminocarbonyloxy-1-phenylethyl)-amino, N -[1-(fluorophenyl)ethyl]-amino, N -[1-(fluorophenyl)-2-hydroxyethyl]-amino, N -[1-(acetylamino-phenyl)ethyl]-amino, N -[2-(acetylamino-phenyl)ethyl]-amino, N -(2-hydroxy-1-phenylprop-1-yl)-amino, N -(1-phenylprop-2-yl)-amino, N -(2-phenylprop-2-yl)-amino, N -(1-hydroxy-1-phenylprop-2-yl)-amino, N -(1-hydroxy-3-phenylprop-2-yl)-amino, N -(furylmethyl)-amino, N -(pyridylmethyl)-amino, dimethylamino, N -isobutyl- N -methylamino, N -(2,2-dimethylpropyl)- N -methylamino, N -allyl- N -methylamino, N -(3,3-dimethylprop-2-en-1-yl)- N -methylamino, N -(1-cyclohexylethyl)- N -methylamino, N -benzyl- N -methylamino, N -methyl- N -(methylbenzyl)-amino, N -(fluorobenzyl)- N -methylamino, N -(acetylamino-benzyl)- N -methylamino, N -(1-phenylethyl)-amino, N -methyl- N -(2-phenylethyl)-amino, N -(2-hydroxy-1-phenylethyl)- N -methylamino, N -(2-methoxy-1-phenylethyl)- N -methylamino, N -[2-(acetylamino-phenyl)ethyl]- N -methylamino, N -(furylmethyl)- N -methylamino, N -methyl- N -(thienylmethyl)-amino, N -benzyl- N -(2-hydroxyethyl)-amino, N,N -bis(furylmethyl)-amino, 3,3-dimethylpiperidinyl, 2-phenylpiperidinyl, 3-hydroxy-2-phenylpiperidinyl and 1,2,3,4-tetrahydroisoquinolin-2-yl.
- 20 Particular examples of R^1 include benzyloxy, N -[1-(fluorophenyl)-2-hydroxyethyl]-amino and N -benzyl- N -methylamino.

Representative values of the group R include hydroxy, benzyloxy, benzyloxymethyl, methoxy-benzyloxy, pyridylmethoxy, benzylthio-methyl, fluorobenzylthio-methyl, phenylsulphinylmethyl, benzylsulphinylmethyl, fluorobenzyl-sulphinyl, fluorobenzyl-sulphinylmethyl, fluorobenzyl-
5 sulphonylmethyl, indanyl-amino, indanylaminomethyl, hydroxyindanyl-amino, benzylamino, benzylaminomethyl, 1-(N-benzylamino)-2-hydroxyethyl, N-(methylbenzyl)-aminomethyl, N-(acetylamino-benzyl)-amino, N-(acetylamino-benzyl)-aminomethyl, N-(1-phenylethyl)-amino, N-(1-phenylethyl)-aminomethyl, N-(2-phenylethyl)-aminomethyl, N-(2-
10 hydroxy-1-phenylethyl)-amino, N-(2-hydroxy-1-phenylethyl)-aminomethyl, N-(2-methoxy-1-phenylethyl)-amino, N-(2-aminocarbonyloxy-1-phenylethyl)-amino, N-[1-(fluorophenyl)ethyl]-amino, N-[1-(fluorophenyl)-2-hydroxyethyl]-amino, N-[1-(fluorophenyl)-2-methoxyethyl]-amino, N-[1-(acetylamino-phenyl)ethyl]-amino, N-[1-(acetylamino-phenyl)ethyl]-
15 aminomethyl, N-[2-(acetylamino-phenyl)ethyl]-amino, N-(2-hydroxy-1-phenylprop-1-yl)-amino, N-(1-phenylprop-2-yl)-amino, N-(2-phenylprop-2-yl)-aminomethyl, N-(1-hydroxy-1-phenylprop-2-yl)-amino, N-(1-hydroxy-2-phenylprop-2-yl)-amino, N-(1-hydroxy-3-phenylprop-2-yl)-amino, N-(furylmethyl)-amino, N-(furylmethyl)-aminomethyl, N-(pyridylmethyl)-
20 aminomethyl, N-isobutyl-N-methyl-aminomethyl, N-(2,2-dimethylpropyl)-N-methyl-aminomethyl, N-allyl-N-methylamino, N-(3,3-dimethylprop-2-en-1-yl)-N-methylamino, N-(1-cyclohexylethyl)-N-methyl-aminomethyl, N-benzyl-N-methylamino, N-benzyl-N-methyl-aminomethyl, N-methyl-N-(methylbenzyl)-aminomethyl, N-(fluorobenzyl)-N-methylamino, N-(
25 acetylamino-benzyl)-N-methyl-aminomethyl, N-methyl-N-(1-phenylethyl)-aminomethyl, N-methyl-N-(2-phenylethyl)-aminomethyl, N-(2-hydroxy-1-phenylethyl)-N-methylamino, N-(2-hydroxy-1-phenylethyl)-N-methyl-aminomethyl, N-(2-methoxy-1-phenylethyl)-N-methylamino, N-[2-(acetylamino-phenyl)ethyl]-N-methylamino, N-(furylmethyl)-N-methylamino, N-methyl-N-(thienylmethyl)-amino, N-
30 benzyl-N-(2-hydroxyethyl-aminomethyl, N,N-bis(furylmethyl)-amino, 3,3-

- 15 -

dimethylpiperidinylmethyl, 2-phenylpiperidinyl, 2-phenylpiperidinylmethyl, 3-hydroxy-2-phenylpiperidinylmethyl and 1,2,3,4-tetrahydroisoquinolin-2-yl.

Particular values of R include benzyloxy, N-[1-(fluorophenyl)-2-hydroxyethyl]-amino and N-benzyl-N-methylamino.

Suitable values of R^a include hydrogen, hydroxy and benzyl, especially hydrogen.

Suitably, R^a and R^b independently represent hydrogen or methyl, especially hydrogen.

10 Suitably, R^c represents hydrogen or methyl, especially hydrogen.

Suitably, R^d and R^e are independently selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, trifluoromethyl, phenyl, methylphenyl (especially 4-methylphenyl), benzyl and phenethyl.

Suitably, the substituent Z represents hydrogen, fluoro, cyano, hydroxy, methoxy, ethoxy, benzyloxy, methylamino-carbonyloxy, cyano-methoxy, aminocarbonyl-methoxy, methylsulphonyl, aminosulphonyl, N-methylamino-sulphonyl, N,N-dimethylamino-sulphonyl, amino, formylamino, acetylamino, trifluoromethyl-carbonylamino, benzyloxy-carbonylamino, methyl-sulphonylamino, ethyl-sulphonylamino,

20 methylphenyl-sulphonylamino, N-methyl-(N-methylsulphonyl)-amino, N-methyl-(N-ethylsulphonyl)-amino, N-methyl-(N-trifluoromethylsulphonyl)-amino, N-ethyl-(N-methylsulphonyl)-amino, N-benzyl-(N-methylsulphonyl)-amino, acetyl, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl,

25 methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, butylaminocarbonyl, benzylaminocarbonyl or phenethyl-aminocarbonyl; or a group of formula (Za), (Zb), (Zc) or (Zd) as defined above; or an optionally substituted five-membered heteroaromatic ring as specified above.

In a particular embodiment, Z represents -SO₂NR^fR^g in which R^f and R^g are as defined above. In a subset of this embodiment, R^f and R^g independently represent hydrogen or C₁₋₆ alkyl, especially hydrogen or

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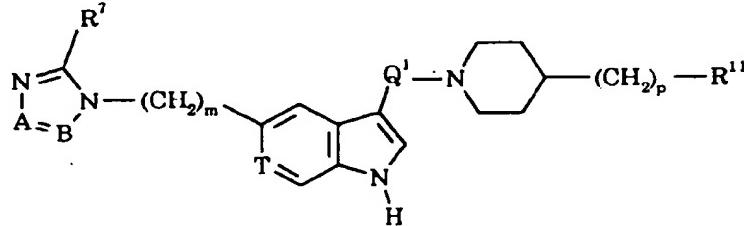
methyl. Particular values of Z in this context include aminosulphonyl, N-methylamino-sulphonyl and N,N-dimethylamino-sulphonyl, especially N-methylamino-sulphonyl.

In another embodiment, Z represents a group of formula (Zb) in which R⁴ is hydrogen or methyl. In a subset of this embodiment, X and Y both represent oxygen. In a particular aspect of this subset, the chiral centre denoted by the asterisk * is in the (S) configuration.

When the group Z represents an optionally substituted five-membered heteroaromatic ring, this is suitably a 1,3-oxazole, 1,3-thiazole, 10 imidazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole or tetrazole ring. Preferably, the ring is a 1,3-oxazole, 1,3-thiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole or 1,2,4-triazole ring, in particular a 1,2,4-triazol-1-yl or 1,2,4-triazol-4-yl moiety.

15 Suitably, the five-membered heteroaromatic ring Z is unsubstituted. Examples of optional substituents which may typically be attached to the moiety Z include methyl, ethyl, benzyl and amino.

A particular sub-class of compounds according to the invention is represented by the compounds of formula II A, and salts and prodrugs 20 thereof:



(IIA)

wherein

25 m is zero, 1, 2 or 3, preferably zero or 1;

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p is zero, 1 or 2;

Q¹ represents a straight or branched alkylene chain containing from 2 to 5 carbon atoms, substituted in any position by one or more fluorine atoms;

- 5 T represents nitrogen or CH;
A represents nitrogen or CH;
B represents nitrogen or C-R⁸;
R⁷ and R⁸ independently represent hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl,
10 heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, halogen, cyano or trifluoromethyl;
R¹¹ represents -OR⁹ or -NR⁹R¹⁰; and
R⁹ and R¹⁰ independently represent hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, indanyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl
15 or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted.

Examples of suitable optional substituents on the groups R⁹ and R¹⁰ include C₁₋₆ alkyl, halogen, cyano, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, aminocarbonyloxy, C₂₋₆ alkylcarbonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulphonylamino and C₁₋₆ alkylaminosulphonylmethyl.

Representative values of R⁹ and R¹⁰ include hydrogen, methyl, hydroxyethyl, isobutyl, 2,2-dimethylpropyl, allyl, dimethylallyl, 1-cyclohexylethyl, 2-cyclohexylethyl, indanyl, hydroxy-indanyl, phenyl, benzyl, methyl-benzyl, fluorobenzyl, methoxy-benzyl, acetylamino-benzyl, 1-phenylethyl, 2-phenylethyl, 2-hydroxy-1-phenylethyl, 2-methoxy-1-phenylethyl, 2-aminocarbonyloxy-1-phenylethyl, 1-(fluorophenyl)ethyl, 1-(fluorophenyl)-2-hydroxyethyl, 1-(fluorophenyl)-2-methoxyethyl, 1-(acetylamino-phenyl)ethyl, 2-(acetylamino-phenyl)ethyl, 2-hydroxy-1-phenylprop-1-yl, 1-phenylprop-2-yl, 2-phenylprop-2-yl, 1-hydroxy-1-

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phenylprop-2-yl, 1-hydroxy-2-phenylprop-2-yl, 1-hydroxy-3-phenylprop-2-yl, furylmethyl, thienylmethyl and pyridylmethyl.

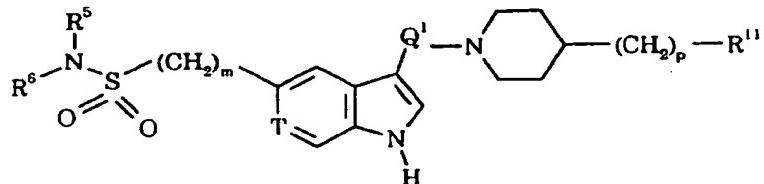
Particular values of R⁹ and R¹⁰ include hydrogen, methyl, benzyl and 1-(fluorophenyl)-2-hydroxyethyl.

5 In relation to formula IIA, the variable p is preferably zero.

Suitably, Q¹ represents a straight or branched 3 or 4 carbon alkylene chain, substituted in any position by one or two fluorine atoms. Where the alkylene linkage Q¹ is substituted by two fluorine atoms, the *gem* difluoro substitution pattern is preferred. Particular alkylene chains 10 for Q¹ include 2-fluoropropylene, 2,2-difluoropropylene and 2-(fluoromethyl)-propylene.

Particular values of R⁷ and R⁸ include hydrogen, methyl, ethyl, benzyl and amino, especially hydrogen.

Another sub-class of compounds according to the invention is 15 represented by the compounds of formula IIB, and salts and prodrugs thereof:



(IIB)

20 wherein

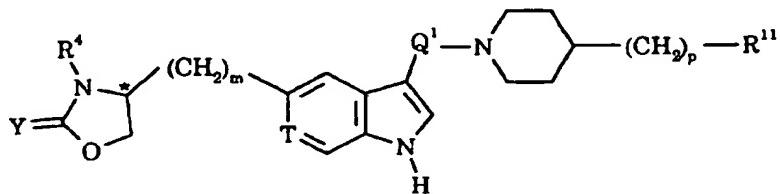
m, p, Q¹, T and R¹¹ are as defined with reference to formula IIA above; and

R⁵ and R⁶ are as defined with reference to formula I above.

Particular values of R⁵ and R⁶ in relation to formula IIB above 25 include hydrogen and C₁₋₆ alkyl, especially hydrogen or methyl. Suitably, one of R⁵ and R⁶ represents hydrogen and the other represents hydrogen or methyl.

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A further sub-class of compounds according to the invention is represented by the compounds of formula IIC, and salts and prodrugs thereof:



5

(IIC)

wherein the asterisk * denotes a chiral centre;

m, p, Q¹, T and R¹¹ are as defined with reference to formula IIA above; and

10 R⁴ and Y are as defined with reference to formula I above.

Particular values of R⁴ in relation to formula IIC include hydrogen and methyl.

Preferably, Y in formula IIC is oxygen.

15 Preferably, the chiral centre denoted by the asterisk * in formula IIC is in the (S) configuration.

In a particular aspect, the present invention provides compounds of formula IIA, IIB and IIC as defined above, and salts and prodrugs thereof, wherein R¹¹ represents a group of formula -NR⁹R¹⁰ in which R⁹ and R¹⁰ are as defined above.

20 Specific compounds within the scope of the present invention include:

4-(N-benzyl-N-methylamino)-1-[2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperidine;

4-[(R)-2-hydroxy-1-(4-fluorophenyl)ethylamino]-1-[2-fluoro-3-(5-(1,2,4-

25 triazol-4-yl)-1H-indol-3-yl]propyl]piperidine;

- 20 -

- 4-(*N*-benzyl-*N*-methylamino)-1-[2,2-difluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
- 4-benzyloxy-1-[2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
- 5 4-benzyloxy-1-[2,2-difluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
- and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain 30 from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or

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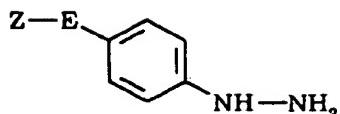
otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an
5 enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl
10 alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed
15 oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

20 In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

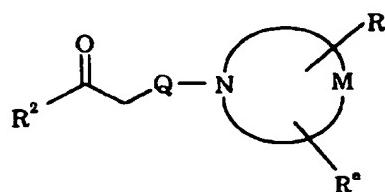
25 The compounds according to the invention wherein T represents CH, U represents C-R² and V represents N-R³, corresponding to the indole derivatives of formula IC as defined above wherein V represents N-R³, may be prepared by a process which comprises reacting a compound of formula III:

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(II)

wherein Z and E are as defined above; with a compound of formula IV, or a carbonyl-protected form thereof:



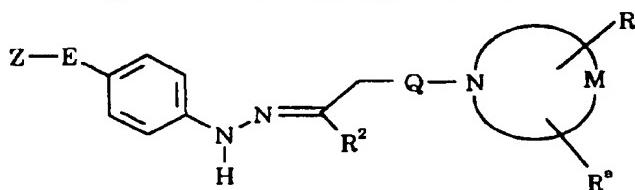
(IV)

- 5 wherein R², Q, M, R and R* are as defined above; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

The reaction between compounds III and IV, which is an example of the well-known Fischer indole synthesis, is suitably carried out by heating the reagents together under mildly acidic conditions, e.g. 4% sulphuric acid at reflux.

Suitable carbonyl-protected forms of the compounds of formula IV include the dimethyl acetal or ketal derivatives.

The Fischer reaction between compounds III and IV may be carried out in a single step, or may proceed via an initial non-cyclising step at a lower temperature to give an intermediate of formula V:

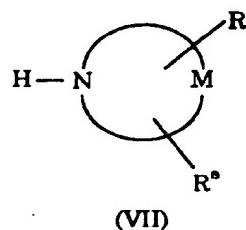
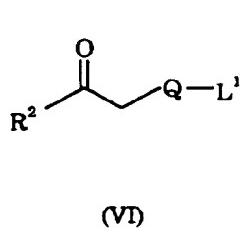


(V)

wherein Z, E, Q, R², M, R and R* are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

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The intermediates of formula IV, or carbonyl-protected forms thereof, may be prepared by procedures analogous to those described in the accompanying Examples, or alternatively by reacting a compound of formula VI, or a carbonyl-protected form thereof, with a compound of 5 formula VII:

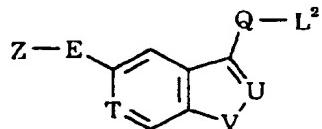


wherein Q, R², M, R and R^a are as defined above, and L¹ represents a suitable leaving group.

10 The leaving group L¹ is suitably a halogen atom, e.g. chlorine or bromine.

Where L¹ represents a halogen atom, the reaction between compounds VI and VII is conveniently effected by stirring the reactants under basic conditions in a suitable solvent, for example sodium carbonate or potassium carbonate in 1,2-dimethoxyethane or N,N-dimethyl-formamide, or triethylamine in tetrahydrofuran or acetonitrile, optionally 15 in the presence of sodium iodide.

In an alternative procedure, the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula VII as defined above with a compound of formula 20 VIII:



(VIII)

wherein Z, E, Q, T, U and V are as defined above, and L² represents a suitable leaving group.

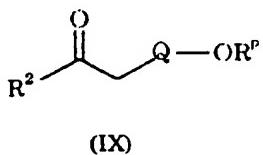
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The leaving group L² is suitably an alkylsulphonyloxy or arylsulphonyloxy group, e.g. methanesulphonyloxy (mesyloxy), trifluoromethanesulphonyloxy (triflyloxy) or p-toluenesulphonyloxy (tosyloxy).

5 Where L² represents an alkylsulphonyloxy or arylsulphonyloxy group, the reaction between compounds VII and VIII is conveniently carried out in a suitable solvent such as isopropanol, 1,2-dimethoxyethane or N,N-dimethylformamide, typically in the presence of a base such as sodium carbonate or potassium carbonate, optionally in the presence of 10 sodium iodide.

The intermediates of formula VIII may be prepared by methods analogous to those described in the accompanying Examples, or by standard procedures well known from the art.

In one representative approach, the compounds of formula VIII 15 wherein T and U both represent CH, V represents NH and L² represents a mesyloxy or tosyloxy group may be prepared by reacting a compound of formula III as defined above with a compound of formula IX:

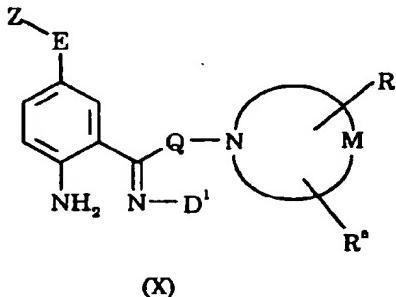


20 wherein Q and R² are as defined above, and R^P represents a hydroxy-protecting group such as *tert*-butyldimethylsilyl; under conditions analogous to those described above for the reaction between compounds III and IV; with removal of the hydroxy-protecting group R^P; followed by 25 mesylation or tosylation of the hydroxy-substituted indole derivative thereby obtained using standard procedures, e.g. treatment with mesyl or tosyl chloride in the presence of a base such as triethylamine or pyridine.

In a further procedure, the compounds according to the invention wherein T represents CH, U represents nitrogen and V represents N-R³,

- 25 -

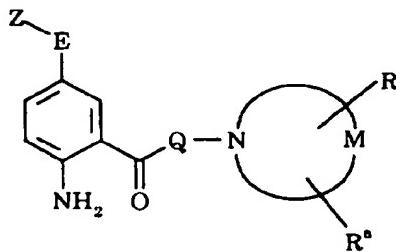
corresponding to the indazole derivatives of formula ID as defined above, may be prepared by a process which comprises cyclising a compound of formula X:



- 5 wherein Z, E, Q, M, R and R^a are as defined above, and D¹ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

The cyclisation of compound X is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of 10 *m*-xylene and 2,6-lutidine at a temperature in the region of 140°C.

The readily displaceable group D¹ in the compounds of formula X suitably represents a C₁₋₄ alkanoyloxy group, preferably acetoxy. Where D¹ represents acetoxy, the desired compound of formula X may be conveniently prepared by treating a carbonyl compound of formula XI:



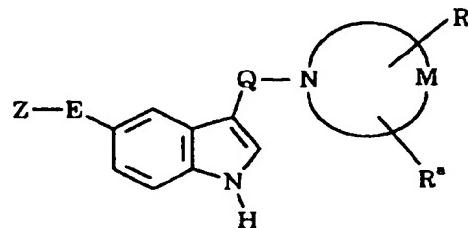
- 15 wherein Z, E, Q, M, R and R^a are as defined above; or a protected derivative thereof, preferably the N-formyl protected derivative; with hydroxylamine hydrochloride, advantageously in pyridine at the reflux temperature of the solvent; followed by acetylation with acetic anhydride,

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advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

The N-formyl protected derivatives of the intermediates of formula XI may conveniently be prepared by ozonolysis of the corresponding indole

5 derivative of formula XII:

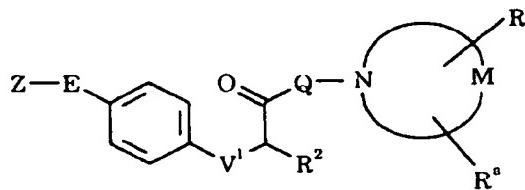


(XII)

wherein Z, E, Q, M, R and R^a are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

The indole derivatives of formula XII may be prepared by methods 10 analogous to those described in the accompanying Examples, or by procedures well known from the art.

In a still further procedure, the compounds according to the invention wherein T represents CH, U represents C-R² and V represents oxygen or sulphur, corresponding to the benzofuran or benzthiophene 15 derivatives of formula IC wherein V is oxygen or sulphur respectively, may be prepared by a process which comprises cyclising a compound of formula XIII:



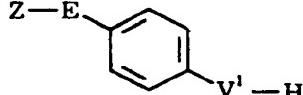
(XIII)

wherein Z, E, Q, R², M, R and R^a are as defined above, and V¹ represents 20 oxygen or sulphur.

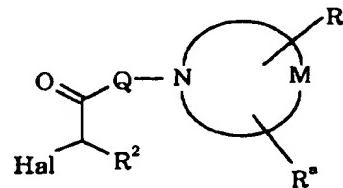
- 27 -

The cyclisation of compound XIII is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

- 5 The compounds of formula XIII may be prepared by reacting a compound of formula XIV with a compound of formula XV:



(XIV)



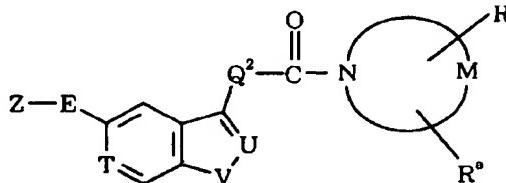
(XV)

wherein Z, E, Q, R², V¹, M, R and R^a are as defined above, and Hal represents a halogen atom.

- 10 The reaction is conveniently effected in the presence of a base such as sodium hydroxide.

The hydroxy and mercapto derivatives of formula XIV may be prepared by a variety of methods which will be readily apparent to those skilled in the art. One such method is described in EP-A-0497512.

- 15 In a yet further procedure, the compounds according to the invention may be prepared by a process which comprises reducing a compound of formula XVI:



(XVI)

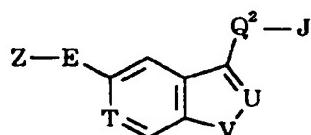
wherein Z, E, T, U, V, M, R and R^a are as defined above, and -Q²-CH₂- corresponds to the moiety Q as defined above.

- 20 The reaction is suitably carried out by treating the compound of formula XVI with a reducing agent such as lithium aluminium hydride in

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an appropriate solvent, e.g. diethyl ether, tetrahydrofuran or mixtures thereof.

The compounds of formula XVI above may suitably be prepared by reacting a compound of formula VII as defined above with the appropriate 5 compound of formula XVII:



(XVII)

wherein Z, E, T, U, V and Q² are as defined above, and J represents a reactive carboxylate moiety.

Suitable values for the reactive carboxylate moiety J include esters, 10 for example C₁₋₄ alkyl esters; acid anhydrides, for example mixed anhydrides with C₁₋₄ alkanoic acids; acid halides, for example acid chlorides; and acylimidazoles.

By way of example, the intermediates of formula XVII above wherein J is an acid chloride moiety may be prepared by treating the 15 corresponding carboxylic acid derivative with thionyl chloride in toluene. Similarly, the intermediates of formula XVII wherein J is an acylimidazole moiety may be prepared by treating the corresponding carboxylic acid derivative with 1,1'-carbonyldiimidazole. Alternatively, the reactive 20 carboxylate moiety J may be obtained by treating the corresponding compound wherein J is carboxy with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, optionally in the presence of triethylamine; the resulting activated carboxylate intermediate may then suitably be reacted *in situ* with the required compound of formula VII.

25 The hydrazine derivatives of formula III above may be prepared by methods analogous to those described in WO-A-91/18897, WO-A-94/02477, EP-A-0438230, EP-A-0497512 and EP-A-0548813.

Where they are not commercially available, the starting materials of formula VI, VII, IX, XV and XVII may be prepared by the methods described in the accompanying Examples, or by analogous procedures which will be apparent to those skilled in the art.

- 5 It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I wherein R^x is benzyl initially obtained may be converted into a compound
- 10 of formula I wherein R^x is hydrogen typically by conventional catalytic hydrogenation, or by transfer hydrogenation using a hydrogenation catalyst such as palladium on charcoal in the presence of a hydrogen donor such as ammonium formate. Moreover, a compound of formula I wherein R¹ is hydroxy initially obtained may be converted into the
- 15 corresponding carbonyl compound (aldehyde or ketone) by treatment with a conventional oxidising agent such as sulphur trioxide-pyridine complex; the resulting carbonyl compound may then be converted in turn into a compound of formula I wherein R¹ represents -NHR^y, suitably by a standard reductive amination procedure which comprises treating the
- 20 carbonyl compound with the appropriate amine of formula R^y-NH₂ in the presence of a suitable reducing agent, typically sodium cyanoborohydride. Alternatively, the carbonyl compound may be converted into a compound of formula I wherein R represents -CH₂-SOR^x and R^x represents hydroxy by treatment of the carbonyl compound with the anion of CH₂-SOR^x.
- 25 Furthermore, a compound of formula I wherein R¹ represents -NHR^y initially obtained may be converted into a further compound of formula I wherein R¹ represents -NR^xR^y, in which R^x corresponds to the group -CH₂R^z, suitably by a reductive amination procedure which comprises treating the compound of formula I wherein R¹ represents -NHR^y with the
- 30 appropriate aldehyde of formula R^z-CHO in the presence of a reducing agent such as sodium cyanoborohydride. In addition, a compound of

- 30 -

formula I wherein R³ is hydrogen initially obtained may be converted into a compound of formula I wherein R³ represents C₁₋₆ alkyl by standard alkylation techniques, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in

- 5 N,N-dimethylformamide.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be
10 prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such
15 as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

20 During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene &
25 P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

- 30 The compounds in accordance with the present invention potently and selectively bind to the 5-HT_{1Dα} receptor subtype, inhibit forskolin-

stimulated adenylyl cyclase activity, and stimulate [³⁵S]-GTP γ S binding to membranes from clonal cell lines expressing human cloned receptors.

5-HT_{1D_a}/5-HT_{1D_b} Radioligand Binding

5

Chinese hamster ovary (CHO) clonal cell lines expressing the human 5-HT_{1D_a} and 5-HT_{1D_b} receptors were harvested in PBS and homogenised in ice cold 50 mM Tris-HCl (pH 7.7 at room temperature) with a Kinematica polytron and centrifuged at 48,000g at 4°C for 11 min.

10 The pellet was then resuspended in 50 mM Tris-HCl followed by a 10 min incubation at 37°C. Finally the tissue was recentrifuged at 48,000g, 4°C for 11 min and the pellet resuspended, in assay buffer (composition in mM: Tris-HCl 50, pargyline 0.01, CaCl₂ 4; ascorbate 0.1%; pH 7.7 at room temperature) to give the required volume immediately prior to use (0.2 mg

15 protein/ml). Incubations were carried out for 30 min at 37°C in the presence of 0.02-150 nM [³H]-5-HT for saturation studies or 2-5 nM [³H]-5-HT for displacement studies. The final assay volume was 1 ml. 5-HT (10 μ M) was used to define non-specific binding. The reaction was initiated by the addition of membrane and was terminated by rapid

20 filtration through Whatman GF/B filters (presoaked in 0.3% PEI/ 0.5% Triton X) followed by 2 x 4 ml washings with 50 mM Tris-HCl. The radioactive filters were then counted on a LKB beta or a Wallac beta plate counter. Binding parameters were determined by non-linear, least squares regression analysis using an iterative curve fitting routine, from

25 which IC₅₀ (the molar concentration of compound necessary to inhibit binding by 50%) values could be calculated for each test compound. The IC₅₀ values for binding to the 5-HT_{1D_a} receptor subtype obtained for the compounds of the accompanying Examples were below 50 nM in each case. Furthermore, the compounds of the accompanying Examples were all

30 found to possess a selective affinity for the 5-HT_{1D_a} receptor subtype of at least 10-fold relative to the 5-HT_{1D_b} subtype.

5-HT_{1D_a}/5-HT_{1D_b} Adenylyl Cyclase Assay

Studies were performed essentially as described in *J. Pharmacol. Exp. Ther.*, 1986, 238, 248. CHO clonal cell lines expressing the human cloned 5-HT_{1D_a} and 5-HT_{1D_b} receptors were harvested in PBS and homogenised, using a motor driven teflon/glass homogeniser, in ice cold Tris HCl-EGTA buffer (composition in mM: Tris HCl 10, EGTA 1, pH 8.0 at room temperature) and incubated on ice for 30-60 min. The tissue was then centrifuged at 20,000g for 20 min at 4°C, the supernatant discarded and the pellet resuspended in Tris HCl-EDTA buffer (composition in mM: Tris HCl 50, EDTA 5, pH 7.6 at room temperature) just prior to assay. The adenylyl cyclase activity was determined by measuring the conversion of α-[³³P]-ATP to [³³P]-cyclic AMP. A 10 µl aliquot of the membrane suspension was incubated, for 10-15 min, in a final volume of 50 µl, at 30°C, with or without forskolin (10 µM), in the presence or absence of test compound. The incubation buffer consisted of 50 mM Tris HCl (pH 7.6 at room temperature), 100 mM NaCl, 30 µM GTP, 50 µM cyclic AMP, 1 mM dithiothreitol, 1 mM ATP, 5 mM MgCl₂, 1 mM EGTA, 1 mM 3-isobutyl-1-methylxanthine, 3.5 mM creatinine phosphate, 0.2 mg/ml creatine phosphokinase, 0.5-1 µCi α-[³³P]-ATP and 1 nCi [³H]-cyclic AMP. The incubation was initiated by the addition of membrane, following a 5 min preincubation at 30°C, and was terminated by the addition of 100 µl SDS (composition in mM: sodium lauryl sulphate 2%, ATP 45, cyclic AMP 1.3, pH 7.5 at room temperature). The ATP and cyclic AMP were separated on a double column chromatography system (*Anal. Biochem.*, 1974, 58, 541). Functional parameters were determined using a least squares curve fitting programme ALLFIT (*Am. J. Physiol.*, 1978, 235, E97) from which E_{max} (maximal effect) and EC₅₀ (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay,

the EC₅₀ values for the 5-HT_{1D_a} receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT_{1D_a} receptor
5 subtype relative to the 5-HT_{1D_b} subtype.

5-HT_{1D_a}/5-HT_{1D_b} GTP γ S Binding

Studies were performed essentially as described in *Br. J.*

- 10 *Pharmacol.*, 1993, **109**, 1120. CHO clonal cell lines expressing the human cloned 5-HT_{1D_a} and 5-HT_{1D_b} receptors were harvested in PBS and homogenised using a Kinematica polytron in ice cold 20 mM HEPES containing 10 mM EDTA, pH 7.4 at room temperature. The membranes were then centrifuged at 40,000g, 4°C for 15 min. The pellet was then
15 resuspended in ice cold 20 mM HEPES containing 0.1 mM EDTA, pH 7.4 at room temperature and recentrifuged at 40,000g, 4°C for 15-25 minutes. The membranes were then resuspended in assay buffer (composition in mM: HEPES 20, NaCl 100, MgCl₂ 10, pargyline 0.01; ascorbate 0.1%; pH 7.4 at room temperature) at a concentration of 40 µg protein/ml for the
20 5-HT_{1D_a} receptor transfected cells and 40-50 µg protein/ml for the 5-HT_{1D_b} receptor transfected cells. The membrane suspension was then incubated, in a volume of 1 ml, with GDP (100 µM for 5-HT_{1D_a} receptor transfected cells, 30 µM for the 5-HT_{1D_b} receptor transfected cells) and test compound at 30°C for 20 min and then transferred to ice for a further 15 min.
25 [³⁵S]-GTP γ S was then added at a final concentration of 100 pM and the samples incubated for 30 min at 30°C. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters and washed with 5 ml water. The radioactive filters were then counted on a LKB beta counter. Functional parameters
30 were determined by a non-linear, least squares regression analysis using an iterative curve fitting routine, from which E_{max} (maximal effect) and

- EC₅₀ (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC₅₀ values for the 5-HT_{1D_a} receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT_{1D_a} receptor subtype relative to the 5-HT_{1D_b} subtype.

10

INTERMEDIATE 14-(1,2,4-Triazol-4-yl)phenylhydrazine

Prepared as described in WO 94/03446.

15

INTERMEDIATE 2(R,S)-2-Fluoro-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol

- a) (R,S)-2-Fluoro-5-hexen-1-ol
- To a cooled (-10°C) and stirred mixture of hydrogen fluoride-pyridine (70% HF; 10ml) and anhydrous dichloromethane (60ml), in a polypropylene tube, was added dropwise *via* syringe neat 1,2-epoxy-5-hexene (13.8ml) over 20 minutes, under nitrogen. After a further 20 minutes, the yellow solution was carefully poured into ice-water-concentrated ammonia (57ml of ammonia; total volume 400ml) and the aqueous mixture was saturated with solid sodium chloride. Products were extracted with diethyl ether (2x500ml) and the combined ethereal solutions were washed with brine (45ml), brine - 10% aqueous sodium bicarbonate (5:1, 60ml), then dried (MgSO₄) and concentrated (bath temperature 30°C). Flash chromatography of the residual liquid (silica gel, hexane - diethyl ether, 65:35), followed by purification on alumina

(activity III, dichloromethane), gave 4.4g of the *title compound* as a colourless liquid; δ_H (360MHz, CDCl₃) 1.56-1.90 (2H, m), 2.10-2.30 (2H, m), 3.62-3.80 (2H, m), 4.48-4.70 (1H, dm, J=50Hz), 5.00-5.12 (2H, m), 5.75-5.88 (1H, m).

5

b) (R,S)-6-tert-Butyldimethylsilyloxy-5-fluoro-1-hexene

To a stirred solution of 2-fluoro-5-hexen-1-ol (4.4g, 37.2mmol) in anhydrous dimethylformamide (125ml) were added imidazole (7.60g, 111.7mmol) and *tert*-butyldimethylsilyl chloride (8.42g, 55.9mmol), under nitrogen. After being stirred at room temperature for 7.5 hours, the mixture was diluted with diethyl ether (400ml) and it was washed with water (150ml), 1M hydrochloric acid (100ml), 5% aqueous sodium bicarbonate (100ml), brine (100ml), then dried (MgSO₄) and concentrated. Flash chromatography of the residue (silica gel, petrol ether (40-60) to petrol ether (40-60) - 5% diethyl ether) gave the *title compound* as a colourless liquid. Some impure fractions were repurified on alumina (activity III; petroleum ether (40-60)); total yield of product 6.72g (77.7%); δ_H (360MHz, CDCl₃) 0.07 (6H, s), 0.90 (9H, s), 1.58-1.84 (2H, m), 2.10-2.30 (2H, m), 3.71 (2H, dd, J=22.2 and 4.7Hz), 4.40-4.60 (1H, dm, J=49Hz), 4.96-5.10 (2H, m), 5.75-5.88 (1H, m).

10

15

20

c) (R,S)-5-tert-Butyldimethylsilyloxy-4-fluoropentanal

Ozone was bubbled through a cooled (-75°C) and stirred solution of the preceding olefin (6.7g, 28.8mmol) in anhydrous dichloromethane (150ml) until a blue colour persisted (45 minutes). Oxygen was then bubbled for 10 minutes through the solution before it was kept under a nitrogen atmosphere. Anhydrous dimethyl sulfide (10ml, 136.2mmol) was added at -78°C and the mixture was allowed to warm to room temperature. After 2 hours, solvents were removed under vacuum (bath temperature 32°C) and the residue was purified by flash chromatography (silica gel, hexane - diethyl ether, 80:20) to give 5.45g of the intermediate

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ozonide and 1 g of the *required title product*, as pale pink liquids. The ozonide (5.4g, 19.28mmol) in anhydrous dichloromethane (125ml) was cooled to -78°C, under nitrogen, and anhydrous triethylamine (5.4ml, 38.6mmol) was added over 2 minutes. The resulting solution was allowed 5 to warm to room temperature and stirred for 2.5 hours. The mixture was half concentrated under vacuum and directly chromatographed on silica gel (dichloromethane) to give 3.60g of the *title compound* as a colourless liquid; δ_H (360MHz, CDCl₃) 0.07 (6H, s), 0.90 (9H, s), 1.90-2.05 (2H, m), 2.54-2.72 (2H, m), 3.73 (2H, dd, J=21.3 and 4.5Hz), 4.40-4.62 (1H, dm, 10 J=49.5Hz), 9.81 (1H, dd, J=2.1 and 0.9Hz).

d) (R,S)-2-Fluoro-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol

To a stirred solution of the preceding aldehyde (4.60g, 19.6mmol) in dioxane (170ml) was added 4-(1,2,4-triazol-4-yl)phenylhydrazine (3.80g, 15 21.1mmol) followed by water (20ml). After 15 minutes, 2M hydrochloric acid (11ml) was added and the mixture was refluxed for 68 hours under nitrogen. Solvents were removed under vacuum and the residue was purified by flash chromatography (silica gel, dichloromethane - methanol, 90:10), then alumina (activity III, dichloromethane - methanol - ammonia, 20 95:5:0.5; then dichloromethane - methanol - ammonia, 90:10:1), to give 700mg of the *title compound* as a yellow solid; δ_H (360MHz, DMSO-d₆) 2.98-3.10 (2H, m), 3.44-3.66 (2H, m), 4.66-4.88 (1H, dm, J=49Hz), 4.93 (1H, t, J=5.6Hz), 7.32 (1H, dd, J=8.5 and 1.9Hz), 7.35 (1H, d, J=2.1Hz), 7.50 (1H, d, J=8.5Hz), 7.82 (1H, d, J=1.9Hz), 9.00 (2H, s), 11.19 (1H, s); 25 m/e (ES) 261 (M⁺⁺1).

EXAMPLE 1

30 4-(N-Benzyl-N-methylamino)-1-{(R,S)-2-fluoro-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine, 2.25 Hydrogen Oxalate, 1.0 Hydrate

- a) 1-tert-Butyloxycarbonyl-4-(N-benzyl-N-methylamino)piperidine
- To a stirred solution of 1-*tert*-butyloxycarbonyl-4-piperidone (3.30g, 16.5mmol) and benzylamine (1.64ml, 15.0mmol) in a mixture of methanol (150ml) and glacial acetic acid (3.4ml, 60mmol) was added sodium cyanoborohydride (1.04g, 16.5mmol), and the resulting mixture was stirred at room temperature for 2 hours 15 minutes. A solution of formaldehyde (38% w/v aqueous solution; 1.42ml) in methanol (5ml) was added and stirring was continued for 16 hours. 4N Sodium hydroxide (35ml) was added and the methanol was removed under vacuum. The residue was diluted with water (50ml) and products were extracted with diethyl ether (2x300ml). The combined organic phases were washed with brine (50ml), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane - methanol - ammonia, 97:3:0.2) followed by repurification of impure fractions on alumina (activity III, dichloromethane) afforded 3.98g (87.4%) of the *title compound* as a colourless thick oil; δ_{H} (360MHz, CDCl_3) 1.46 (9H, s), 1.44-1.56 (2H, m), 1.76-1.85 (2H, m), 2.20 (3H, s), 2.52-2.76 (3H, m), 3.57 (2H, s), 4.10-4.22 (2H, m), 7.20-7.36 (5H, m); m/e (ES) 305 ($M^{+}+1$).
- b) 4-(N-Benzyl-N-methylamino)piperidine
- A solution of the preceding piperidine (3.95g, 12.97mmol) in a mixture of dichloromethane (40ml) and trifluoroacetic acid (40ml) was allowed to stand at room temperature for 3 hours. Solvents were removed under vacuum and the residue azeotroped with toluene-methanol (5:1, 100ml). The remaining residue was dissolved in 4N sodium hydroxide (50ml) and extracted with dichloromethane (2x150ml). The combined organic solutions were washed with brine (50ml), dried (Na_2SO_4) and concentrated to give the *title compound* (2.70g, 100%) which was used in the next step without further purification; δ_{H} (360MHz, CDCl_3) 1.52 (2H, dq, J=12.2 and 4.0Hz), 1.80-1.90 (2H, m), 2.21 (3H, s), 2.50-2.66 (3H, m), 3.12-3.22 (2H, m), 3.58 (2H, s), 7.18-7.36 (5H, m); m/e (ES) 205 ($M^{+}+1$).

c) 4-(N-Benzyl-N-methylamino)-1-{(R,S)-2-fluoro-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 2.25 Hydrogen Oxalate. 1.0 Hydrate

To a stirred suspension of Intermediate 2 (200mg, 0.77mmol) in
5 anhydrous tetrahydrofuran (30ml) was added anhydrous triethylamine
(214 μ l, 1.54mmol) followed by methanesulphonyl chloride (121 μ l,
1.54mmol). After being stirred at room temperature for 2 hours 10
minutes, under nitrogen, the mixture was diluted with ethyl acetate
(125ml), washed with brine-water (1:1, 25ml), brine (25ml), then dried
10 ($MgSO_4$) and concentrated.

A mixture of the mesylate thus obtained, anhydrous potassium
carbonate (128mg) and 4-(N-benzyl-N-methylamino)piperidine (800mg) in
isopropanol (35ml) was refluxed, under nitrogen, for 65 hours. Solvents
were removed under vacuum, the residue was dissolved in water (40ml)
15 and products were extracted with ethyl acetate (2x100ml). The combined
organic solutions were washed with brine (1x40ml), dried (Na_2SO_4) and
concentrated. Flash chromatography of the residue (silica gel,
dichloromethane - methanol - ammonia, 95:5:0.5) followed by purification
on alumina (activity III, dichloromethane - methanol - ammonia, 97:3:0.2),
20 and finally flash chromatography (silica gel, dichloromethane-methanol,
80:20) gave 188mg (54.8%) of the *title compound free base*. The oxalate
salt was prepared from ethanol-diethyl ether, mp 110-117°C. (Found: C,
54.81; H, 5.75; N, 12.55. $C_{26}H_{31}FN_6 \times 2.25C_2H_2O_4 \times 1.0H_2O$ requires: C,
54.91; H, 5.67; N, 12.60%). δ_H (360MHz, D₂O) 2.08-2.24 (2H, m), 2.36-2.48
25 (2H, m), 2.75 (3H, s), 3.10-3.34 (4H, m), 3.38-3.58 (2H, m), 3.62-3.92 (3H,
m), 4.28-4.50 (2H, m), 5.26-5.48 (1H, m), 7.32 (1H, d, J=8.7Hz), 7.40-7.55
(6H, m), 7.62 (1H, d, J=8.7Hz), 7.77 (1H, s), 8.92 (2H, s); m/e (ES) 447
(M⁺⁺¹).

EXAMPLE 2

1-{(R,S)-2-Fluoro-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(R)-2-hydroxy-1-(4-fluorophenyl)ethyl]amino}piperidine. 2.0 Hydrogen Oxalate.
1.2 Hydrate.

a) (R)-2-Amino-2-(4-fluorophenyl)ethanol

To a stirred 1.0M solution of lithium aluminium hydride in THF (23.5ml, 23.5mmol), cooled to 0°C under Ar, was added portionwise over 1h 45min solid (-)-4-fluoro-D- α -phenylglycine (1.98g, 11.7mmol). The reaction mixture was then stirred at room temperature overnight before carefully adding water (0.89ml), then 4N NaOH solution (0.89ml) and then water (2.68ml). The mixture was stirred for a few minutes, then filtered, and the filtrate was evaporated *in vacuo*. Flash chromatography of the residue (silica gel, dichloromethane - methanol - ammonia, 90:10:1) gave 1.499g (82%) of the *title compound* as a white solid; δ_H (250MHz, CDCl₃) 3.52 (1H, dd, J=10.7 and 8.2Hz), 3.71 (1H, dd, J=10.7 and 4.4Hz), 4.06 (1H, dd, J=8.1 and 4.4Hz), 6.99-7.08 (2H, m), 7.28-7.34 (2H, m).

20

b) 1-tert-Butyloxycarbonyl-4-[(R)-2-hydroxy-1-(4-fluorophenyl)ethyl]amino)piperidine

To a stirred solution of 1-*tert*-butyloxycarbonyl-4-piperidone (3.30g, 16.5mmol) and (R)-2-amino-2-(4-fluorophenyl)ethanol (2.33g, 15.0mmol) in a mixture of methanol (150ml) and glacial acetic acid (3.4ml, 60mmol) was added sodium cyanoborohydride (1.04g, 16.5mmol), and the resulting mixture was stirred at room temperature for 18.5 hours. 4N Sodium hydroxide (30ml) was added and the methanol was removed under vacuum. The remaining residue was diluted with water (50ml) and products were extracted with diethyl ether (2x300ml). The combined ethereal phases were washed with brine (50ml), dried (Na₂SO₄) and

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concentrated. Flash chromatography of the residue (silica gel, dichloromethane - methanol - ammonia, 95:5:0.5) gave 4.60g (90.7%) of the title compound as a thick oil which solidified on standing; δ_H (360MHz, CDCl₃) 1.16-1.30 (2H, m), 1.44 (9H, s), 1.58-1.68 (1H, m), 1.84-1.92 (1H, m), 2.48-2.58 (1H, m), 2.66-2.78 (2H, m), 3.45 (1H, dd, J=10.7 and 8.7Hz), 3.65 (1H, dd, J=10.7 and 4.5Hz), 3.90-4.04 (3H, m), 7.00-7.08 (2H, m), 7.22-7.30 (2H, m); m/e (ES) 339 (M⁺+1).

c) 4-[(R)-2-Hydroxy-1-(4-fluorophenyl)ethyl]amino)piperidine

10 The title compound was prepared form the product of the preceding step using a similar method to that described for Example 1, Step b. δ_H (360MHz, CDCl₃+DMSO-d₆) 0.90-1.04 (2H, m), 1.38-1.48 (1H, m), 1.68-1.78 (1H, m), 2.12-2.32 (3H, m), 2.72-2.85 (2H, m), 3.23 (1H, dd, J=10.6 and 8.6Hz), 3.40 (1H, dd, J=10.6 and 4.2Hz), 3.75 (1H, dd, J=8.6 and 4.2Hz), 6.74-6.82 (2H, m), 7.17-7.45 (2H, m); m/e (ES) 239 (M⁺+1).

d) 1-{(R,S)-2-Fluoro-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(R)-2-hydroxy-1-(4-fluorophenyl)ethyl]amino)piperidine. 2.0 Hydrogen Oxalate. 1.2 Hydrate

20 The title compound free base was prepared from the product of the preceding step and Intermediate 2, following a similar procedure to that described for Example 1, step c. The oxalate salt was prepared from ethanol-diethyl ether, mp 130-140°C. (Found: C, 52.77; H, 5.60; N, 12.31. C₂₆H₃₀F₂N₆O x 2.0C₂H₂O₄ x 1.2H₂O requires: C, 52.82; H, 5.38; N, 12.32%).

25 δ_H (360MHz, DMSO-d₆) 1.56-1.78 (2H, m), 1.86-2.04 (2H, m), 2.08-2.32 (2H, m), 2.64-2.82 (3H, m), 2.96-3.10 (4H, m), 3.71 (2H, d, J=5.6Hz), 4.36 (1H, m), 4.96-5.18 (1H, m), 7.22-7.36 (4H, m), 7.50 (1H, d, J=8.6Hz), 7.56-7.60 (2H, m), 7.80 (1H, s), 9.00 (2H, s), 11.26 (1H, s); m/e (ES) 481 (M⁺+1).

EXAMPLE 34-(N-Benzyl-N-methylamino)-1-{2,2-difluoro-3-[5-(1,2,4-triazol-4-yl)-1H-5-indol-3-yl]propyl}piperidine

- a) A solution of hexamethylene tetramine (12 g) and 5-(1,2,4-triazol-4-yl)-1H-indole (10.5 g, 57.1 mmol) in acetic acid (125 ml, 30% v/v) were heated at reflux for 3 hours. The reaction was neutralized with potassium carbonate and the water removed *in vacuo*. The residue was triturated with water and the solid collected to give 5-(1,2,4-triazol-4-yl)-3-(carboxaldehyde)-1H-indole as a brown solid. m/e (ES) 213 ($M^{++}1$).
- b) A suspension of the product from above (1.01 g, 4.8 mmol), N,N-dimethylaminopyridine (DMAP) (47 mg) and di-*tert*-butyldicarbonate (1.03 g), in 25 ml dichloromethane, was stirred for 8 hours. Further quantities of DMAP (50 mg) and di-*tert*-butyldicarbonate (200 mg) were added after 1.5 hours. The reaction was concentrated, and the solid triturated with methanol, to give 5-(1,2,4-triazol-4-yl)-3-(carboxaldehyde)-1-(*tert*-butoxycarbonyl)indole as a beige solid. δ_H (250MHz, d_6 -DMSO) 1.90 (9H, s), 7.96-8.00 (1H, m), 8.46 (1H, d, $J=10$ Hz), 8.54 (1H, d, $J=3$ Hz), 9.03 (1H, s), 9.38 (2H, s), 10.34 (1H, s). m/e (ES) 313 ($M^{++}1$).
- c) A suspension of activated zinc dust (85 mg) and the aldehyde from above (312 mg, 1 mmol) in 3 ml THF and 5 drops DMF was heated to reflux under a nitrogen atmosphere. Ethyl bromodifluoroacetate (0.14 ml, 1.1 mmol) was added. After 15 minutes, a further 0.5 eq of ethyl bromodifluoroacetate was added, followed after 15 minutes by phenyl chlorothionoformate (0.18 ml, 1.3 mmol). The reaction was heated at reflux 1.5 hours, and partitioned between water-ethyl acetate. The combined organic phases were separated, dried ($MgSO_4$), concentrated and

chromatographed using 5% methanol-dichloromethane. The partially purified product was heated to reflux in 15 ml degassed toluene with tributyl tin hydride (0.27 ml, 1 mmol) and α,α' -azobisisobutyronitrile (118 mg). After 2.5 hours, the reaction was concentrated, and

- 5 chromatographed using 2→5% methanol-dichloromethane. Ethyl 2,2-difluoro-3-[5-(1,2,4-triazol-4-yl)-1-*tert*-butoxycarbonylindol-3-yl]propanoate was obtained as a yellow oil. m/e (ES) 421 ($M^{++}+1$). δ_H (250MHz, CDCl₃) 0.92 (3H, t, J=7.5Hz), 1.69 (9H, s), 3.49 (2H, t, J=15Hz), 4.28 (2H, q, J=7.5Hz), 7.30-7.35 (1H, m), 7.56 (1H, m), 7.67 (1H, s), 8.30-10 8.34 (1H, m), 8.50 (2H, s).

- d) A solution of the product from above (179 mg, 0.4 mmol) in 3 ml ethanol was treated with sodium borohydride (20 mg) and the reaction monitored. When all the starting material had reacted, the reaction was quenched by addition of water. The ethanol was removed *in vacuo*, and the product extracted with ethyl acetate. The organic phase was dried (MgSO₄), concentrated and chromatographed using 5% methanol-dichloromethane as eluent. 2,2-Difluoro-3-[5-(1,2,4-triazol-4-yl)-1-*tert*-butoxycarbonylindol-3-yl]propan-1-ol was obtained as a yellow oil. m/e (ES) 379 ($M^{++}+1$). δ_H (250MHz, CDCl₃) 1.69 (9H, s), 3.42 (2H, t, J=17.5Hz), 3.77 (2H, t, J=12.5Hz), 7.30-7.34 (1H, m), 7.69 (1H, s), 7.74 (1H, s), 8.29-20 8.32 (1H, m), 8.60 (2H, br s).

- e) A solution of the product from above (80 mg; 0.21 mmol) in 10 ml anhydrous dichloromethane and pyridine (70 μ l) was cooled to an internal temperature of -50°C under a nitrogen atmosphere. Trifluoromethanesulfonic anhydride (71 μ l) was added, and the reaction allowed to stir at -25→-50°C for 1.5h. Five ml of water was added, and the reaction allowed to attain room temperature. The organic phase was separated, dried (MgSO₄), and concentrated. The crude triflate was dissolved in 3 ml anhydrous DMF and heated 120°C for 10 minutes with

- 43 -

potassium carbonate (58 mg) and the amine from Example 1, step b (86 mg). The reaction was partitioned between ethyl acetate and water. The organic phase was separated, dried (MgSO_4) and concentrated, then deprotected as described in Example 1, step b.

5 The *title compound* free base was obtained by chromatography using 3% methanol-dichloromethane \rightarrow methanol-dichloromethane-ammonia (5:94:1). The salt was prepared as described in Example 1, step c. mp. softens at 85°C. δ_{H} (360MHz, d_6 -DMSO) 1.66-1.80 (2H, m), 1.90-2.00 (2H, m), 2.16-2.24 (2H, m), 2.54 (3H, s), 2.70 (2H, t, $J=14.4\text{Hz}$), 2.90-3.00 (2H, m), 3.06-3.20 (1H, m), 3.44 (2H, t, $J=14.4\text{Hz}$), 4.20-4.28 (2H, m), 7.32-7.60 (8H, m), 7.84 (1H, s), 9.0 (2H, s), 11.4 (1H, s). m/e (ES) 465 ($M^{++}1$).

EXAMPLE 4

15

4-Benzylxyloxy-1-((R,S)-2-fluoro-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine Hydrogen Oxalate

4-Benzylxyloxy piperidine (0.88 g, 4.62 mmol) (Example 5, step b) was reacted as described in Example 1, step c to give the *title compound*, mp. softens at 130°C. (Found: C, 60.13; H, 5.87; N, 12.42. $C_{25}H_{28}FNSO$. $C_2H_2O_4$ requires C, 61.94; H, 5.76; N, 13.38). δ_{H} (360MHz, d_6 -DMSO) 1.60-1.80 (2H, m), 1.80-2.00 (2H, m), 2.54-2.70 (2H, m), 2.80-3.20 (6H, m), 3.46-3.78 (1H, m), 4.50 (2H, s), 5.00-5.24 (1H, m), 7.20-7.40 (7H, m), 7.46-7.56 (1H, m), 7.78 (1H, s), 8.87 (2H, s), 11.04 (1H, s). m/e (ES) 434 ($M^{++}1$).

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EXAMPLE 5

4-Benzylxyloxy-1-{2,2-difluoro-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine

30

- a) A solution of N-*tert*-butoxycarbonylpiperidin-4-ol (25 g, 0.124 mol) in 100 ml anhydrous THF was added to a suspension of sodium hydride (5.96 g, 0.15 mol, pentane washed) in 100 ml anhydrous THF at 0°C. The reaction was stirred at 0°C for 1 hour, then treated with a solution of 5 benzyl bromide (25.65 g, 0.15 mol) in 20 ml anhydrous THF. The reaction was allowed to stand for 20 h at room temperature, cooled to 0°C, and 50 ml water was added cautiously. The product was extracted using ethyl acetate, the combined organic extracts were washed with water, dried (MgSO₄) and concentrated. Chromatography using petroleum ether→20% 10 ethyl acetate-petroleum ether gave 4-benzyloxy-1-*tert*-butoxycarbonyl-piperidine as a colourless solid. δ_H (250MHz, CDCl₃) 1.45 (9H, s), 1.51-1.65 (2H, m), 1.80-1.94 (2H, m), 3.04-3.15 (2H, m), 3.51-3.61 (1H, m), 3.70-3.84 (2H, m), 4.56 (2H, m), 7.26-7.35 (5H, m). m/e (ES) 292.
- 15 b) The product from above (6.1 g, 21 mmol) was reacted as described in Example 1, step b to give 4-benzyloxypiperidine as a crystalline solid. δ_H (360MHz, CDCl₃) 1.43-1.57 (2H, m), 1.91-2.09 (2H, m), 2.55-2.66 (2H, m), 3.06-3.15 (2H, m), 3.41-3.52 (1H, m), 4.56 (2H, s), 7.12-7.37 (5H, m). m/e (ES) 192 (M⁺⁺¹).
- 20 c) Ethyl bromodifluoroacetate (32.07 g, 0.158 mol) and 4-benzyloxy-piperidine (27.36 g) were stirred at room temperature in ethanol overnight. Ethanol and excess reagents were removed *in vacuo* and the residue was chromatographed using 10% ethyl acetate-petroleum ether as 25 eluent to give 1-(2-bromo-2,2-difluoroacetamido)-4-benzyloxypiperidine. δ_H (250MHz, CDCl₃) 1.54-1.92 (4H, m), 3.60-3.87 (5H, m), 4.56 (2H, s), 7.25-7.38 (5H, m).
- d) A solution of allyltributyl tin (17.7 ml) and the product from above 30 (19.9 g, 0.057 mol) in 200 ml of degassed toluene was heated to reflux under a nitrogen atmosphere in the presence of α,α'-azobisisobutyronitrile

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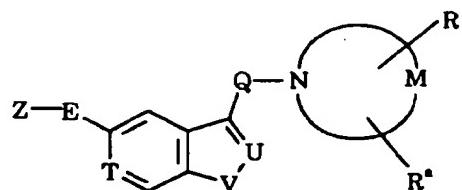
- (0.5 g) for 48 h. Further aliquots of AIBN were added, and refluxing was continued until the reaction had gone to completion. The reaction was concentrated and chromatographed using 5% ethyl acetate-petroleum ether to give 1-(2,2-difluoro-4-pentenamido)-4-benzyloxypiperidine. δ_H (360MHz, CDCl₃) 1.72-1.76 (2H, m), 1.86-1.91 (2H, m), 2.85-2.97 (2H, dt, J=18 and 7.2Hz), 3.44-3.60 (2H, m), 3.67-3.71 (1H, m), 3.80-3.96 (2H, m), 4.56 (2H, s), 5.23 (1H, s), 5.26 (1H, d, J=7.2Hz), 5.81-5.92 (1H, m), 7.25-7.35 (5H, m). m/s (ES) 310 (M⁺⁺¹).
- 5 e) A solution of the product from above (7.0 g, 0.023 mol) in 20 ml anhydrous THF was treated with 9-BBN (182 ml of 0.5M solution) and was heated to reflux for 8h. The reaction was cooled, and carefully basified to pH11-12 using 4N NaOH. Hydrogen peroxide (30% w/v solution, 7.82 g, 26 ml) was added slowly to the cooled reaction. The 10 reaction was allowed to stand for 18h, adjusted to pH8-9, poured into water, and extracted with diethyl ether. The organic extracts were washed with brine, water, dried (MgSO₄) and concentrated *in vacuo*. Purification by chromatography using 10% ethyl acetate petroleum ether as eluent gave 1-(2,2-difluoro-5-hydroxypentan-1-yl)-4-
- 15 benzylxypiperidine as a pale yellow oil. δ_H (250MHz, CDCl₃) 1.60-2.20 (8H, m), 1.36-2.54 (2H, m), 2.70 (2H, t, J=15Hz), 2.84-3.00 (2H, m), 3.40-3.54 (1H, m), 3.68 (2H, t, J=5Hz), 4.53 (2H, s), 7.26-7.35 (5H, m). m/s (ES) 314 (M⁺⁺¹).
- 20 f) A solution of the product from above (3.3 g) in 20 ml anhydrous dimethylsulphoxide was stirred with triethylamine (10.35 ml) at 0°C under a nitrogen atmosphere. Sulphur trioxide-pyridine (2.51 g) was added in portions. The reaction was stirred at room temperature for 1½ hours, a further portion of SO₃-pyridine (0.2 g) added, and stirring 25 continued for 45 minutes. Water was added carefully, the product extracted into ethyl acetate, the organic phase washed with brine, dried
- 30

(MgSO₄), concentrated and purified by dry flash column chromatography using 10% ethyl acetate-petroleum ether as eluent. 1-(2,2-Difluoro-5-pentanal)-4-benzyloxy piperidine was obtained as a pale yellow oil. δ_H (250MHz, CDCl₃) 1.60-1.80 (2H, m), 1.84-2.00 (2H, m), 2.20-2.46 (6H, m), 5 2.64-2.94 (4H, m), 3.44 (br s, 1H), 4.53 (2H, s), 7.24-7.38 (5H, s), 9.90 (br s, 1H). m/e (ES) 312 (M⁺⁺¹).

g) The product from above was reacted in a similar manner as described for Intermediate 2 step d, using 4% sulfuric acid instead of 10 dioxane-water, to give the *title compound* free base. mp. 169.5-170.3°C (ethanol). (Found: C, 66.14; H, 6.09; N, 15.31. C₂₅H₂₇F₂N₅O requires C, 66.50; H, 6.05; N, 15.51). δ_H (360MHz, d₆-DMSO) 1.49-1.52 (2H, m), 1.80-1.90 (2H, m), 2.22-2.32 (2H, m), 2.60-2.78 (4H, m), 3.31-3.45 (3H, m), 7.26-7.38 (7H, m), 7.50-7.52 (1H, m), 7.81 (1H, s), 8.98 (2H, s), 11.32 (1H, s). 15 m/e (ES) 452 (M⁺⁺¹).

CLAIMS:

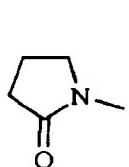
1. A compound of formula I, or a salt or prodrug thereof:



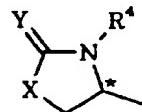
5

wherein

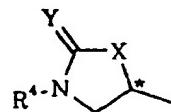
- Z represents hydrogen, halogen, cyano, nitro, trifluoromethyl, -OR⁵,
 -OCOR⁵, -OCONR⁵R⁶, -OCH₂CN, -OCH₂CONR⁵R⁶, -SR⁵, -SOR⁵, -SO₂R⁵,
 10 -SO₂NR⁵R⁶, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁶, -COR⁵, -CO₂R⁵,
 -CONR⁵R⁶, or a group of formula (Za), (Zb), (Zc) or (Zd):



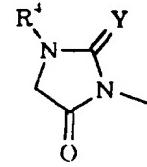
(Za)



(Zb)



(Zc)



(Zd)

- 15 in which the asterisk * denotes a chiral centre; or

Z represents an optionally substituted five-membered

heteroaromatic ring selected from furan, thiophene, pyrrole, oxazole,
 thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole,
 thiadiazole, triazole and tetrazole;

- 20 X represents oxygen, sulphur, -NH- or methylene;

Y represents oxygen or sulphur;

- 48 -

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

Q represents a straight or branched alkylene chain containing from 1 to 6 carbon atoms, substituted in any position by one or more fluorine atoms;

T represents nitrogen or CH;

U represents nitrogen or C-R²;

V represents oxygen, sulphur or N-R³;

R², R³ and R⁴ independently represent hydrogen or C₁₋₆ alkyl;

R⁵ and R⁶ independently represent hydrogen, C₁₋₆ alkyl, trifluoromethyl, phenyl, methylphenyl, or an optionally substituted aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl group; or R⁵ and R⁶, when linked through a nitrogen atom, together represent the residue of an optionally substituted azetidine, pyrrolidine, piperidine, morpholine or piperazine ring;

M represents the residue of an azetidine, pyrrolidine or piperidine ring;

R represents a group of formula -W-R¹;

W represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally substituted in any position by a hydroxy group;

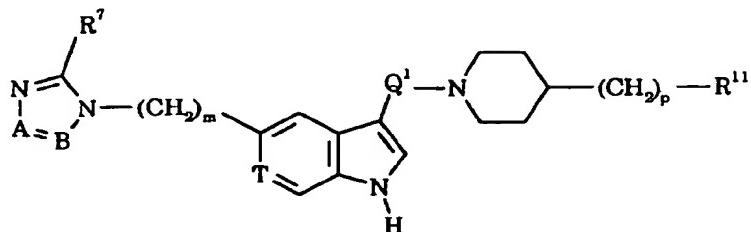
R¹ represents -OR^x, -SR^x, -SOR^x, -SO₂R^x or -NR^xR^y;

R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group; or R^x and R^y together represent a C₂₋₆ alkylene group, which alkylene group may be optionally substituted by one or more substituents selected from C₁₋₆ alkyl, aryl and hydroxy, or fused with a phenyl ring; and

R^a represents hydrogen, hydroxy, hydrocarbon or a heterocyclic group.

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2. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:



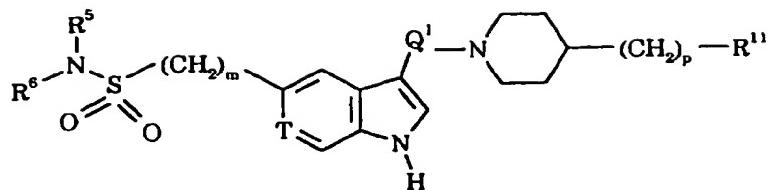
(IIA)

5

wherein

- m is zero, 1, 2 or 3;
 - p is zero, 1 or 2;
 - Q¹ represents a straight or branched alkylene chain containing from 10 2 to 5 carbon atoms, substituted in any position by one or more fluorine atoms;
 - T represents nitrogen or CH;
 - A represents nitrogen or CH;
 - B represents nitrogen or C-R⁸;
 - R⁷ and R⁸ independently represent hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, halogen, cyano or trifluoromethyl;
 - R¹¹ represents -OR⁹ or -NR⁹R¹⁰; and
 - R⁹ and R¹⁰ independently represent hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, indanyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted.
- 25 3. A compound as claimed in claim 1 represented by formula IIB, and salts and prodrugs thereof:

- 50 -



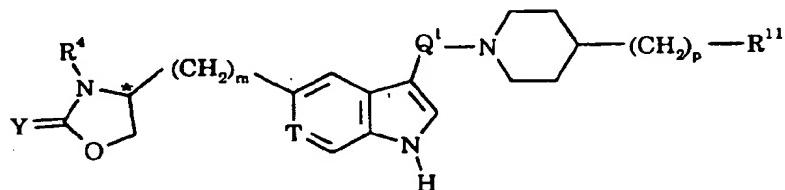
(IIB)

wherein

- 5 m, p, Q¹, T and R¹¹ are as defined in claim 2; and
 R⁶ and R⁴ are as defined in claim 1.

4. A compound as claimed in claim 1 represented by formula IIC, and salts and prodrugs thereof:

10



(IIC)

wherein the asterisk * denotes a chiral centre;

- 15 m, p, Q¹, T and R¹¹ are as defined in claim 2; and
 R⁴ and Y are as defined in claim 1.

5. A compound as claimed in any one of claims 2 to 4 wherein R¹¹ represents a group of formula -NR⁹R¹⁰.

20 6. A compound selected from:

4-(N-benzyl-N-methylamino)-1-[2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperidine;

- 51 -

4-[(*R*)-2-hydroxy-1-(4-fluorophenyl)ethylamino]-1-[2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
and salts and prodrugs thereof.

5 7. A compound selected from:

4-(*N*-benzyl-*N*-methylamino)-1-[2,2-difluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
4-benzyloxy-1-[2-fluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
10 4-benzyloxy-1-[2,2-difluoro-3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
and salts and prodrugs thereof.

15 8. A pharmaceutical composition comprising a compound of
formula I as defined in claim 1 or a pharmaceutically acceptable salt
thereof or a prodrug thereof in association with a pharmaceutically
acceptable carrier.

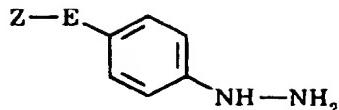
20 9. A compound as claimed in any one of claims 1 to 7 for use in
therapy.

25 10. The use of a compound as claimed in any one of claims 1 to 7
for the manufacture of a medicament for the treatment and/or prevention
of clinical conditions for which an agonist of 5-HT_{1D} receptors selective for
the 5-HT_{1D} subtype thereof is indicated.

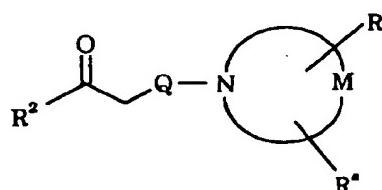
11. A process for the preparation of a compound as claimed in
claim 1, which comprises:

30 (A) reacting a compound of formula III:

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wherein Z and E are as defined in claim 1; with a compound of formula IV, or a carbonyl-protected form thereof:

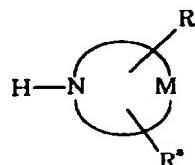


(IV)

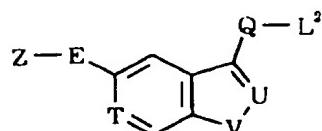
- 5 wherein R², Q, M, R and R* are as defined in claim 1; followed, where required, by N-alkylation by standard methods to introduce the moiety R³;
or

(B) reacting a compound of formula VII:

10



wherein R and R* are as defined in claim 1;
with a compound of formula VIII:



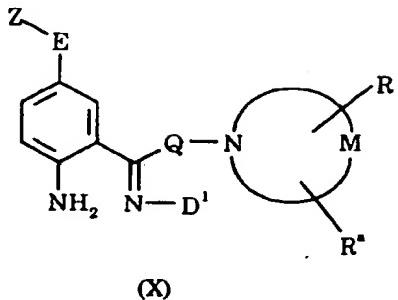
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(VIII)

wherein Z, E, Q, T, U and V are as defined in claim 1, and L² represents a suitable leaving group; or

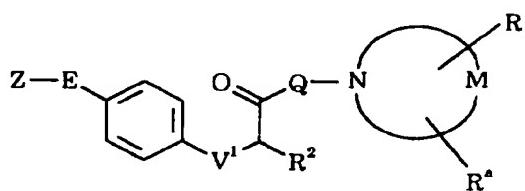
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(C) cyclising a compound of formula X:



wherein Z, E, Q, M, R and R^a are as defined in claim 1, and D¹ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³; or

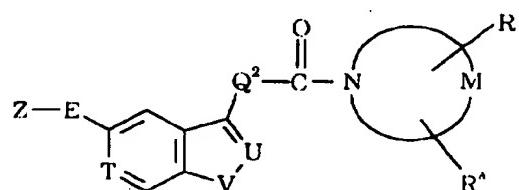
(D) cyclising a compound of formula XIII:



(XIII)

wherein Z, E, Q, R², M, R and R^a are as defined in claim 1, and V¹ represents oxygen or sulphur; or

(E) reducing a compound of formula XVI:



(XVI)

wherein Z, E, T, U, V, M, R and R^a are as defined in claim 1, and -Q²-CH₂- corresponds to the moiety Q as defined in claim 1; and

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/GB 96/02764

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/14 C07D401/06 C07D413/14 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 24105 A (MERCK SHARP & DOHME LTD.) 27 October 1994 see claims ---	1-12
A	WO 94 21627 A (MERCK SHARP & DOHME LTD.) 29 September 1994 see claims ---	1-12
A	WO 94 02477 A (MERCK SHARP & DOHME LTD.) 3 February 1994 cited in the application see claims ---	1-12
P,A	WO 96 04274 A (MERCK SHARP & DOHME LTD.) 15 February 1996 see claims -----	1-12

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- 'Z' document member of the same patent family

Date of the actual completion of the international search 15 January 1997	Date of mailing of the international search report 24.01.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+ 31-70) 340-3016	Authorized officer Chouly, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 96/02764

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 12 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat'l Application No
PCT/GB 96/02764

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9424105	27-10-94	AU-A-	6435594	08-11-94

WO-A-9421627	29-09-94	AU-A-	6215594	11-10-94
		US-A-	5576336	19-11-96

WO-A-9402477	03-02-94	AU-B-	672802	17-10-96
		AU-A-	4578593	14-02-94
		CA-A-	2138649	03-02-94
		EP-A-	0651749	10-05-95
		JP-T-	7509452	19-10-95
		US-A-	5567726	22-10-96

WO-A-9604274	15-02-96	AU-A-	3182495	04-03-96
